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May 27, 2003

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Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Via Hand Carry
to Group Art Unit 1626
Examiner G. Shameem

Mail Stop Issue Fee

Re: U.S. Utility Patent Application
Appl. No. 09/814,123; Filed: March 22, 2001
For: **Aryl Substituted Pyrazoles, Triazoles and Tetrazoles, and the Use Thereof**
Inventors: HOGENKAMP *et al.*
Our Ref: 1861.1270001/JMC/THN

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Amendment Under 37 C.F.R. § 1.312;

2. One sheet of drawings (Figs. 1A-1D); and

3. One (1) return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

John M. Covert
Attorney for Applicants
Registration No. 38,759

Enclosures

SKGF_DC1:137220.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 2060
HOGENKAMP *et al.*	Art Unit: 1626
Appl. No. 09/814,123	Examiner: Shameem, G.
Filed: March 22, 2001	Atty. Docket: 1861.1270001/JMC/THN
For: **Aryl Substituted Pyrazoles, Triazoles and Tetrazoles, and the Use Thereof**	

Amendment Under 37 C.F.R. § 1.312

Commissioner for Patents
Washington, D.C. 20231

Mail Stop Issue Fee

Sir:

In reply to the Examiner's request during a telephone conference of May 22, 2003, submitted herewith is an Amendment Under 37 C.F.R. § 1.312. As payment of the issue fee has not yet been made or is filed herewith, Applicants respectfully submit that filing under 37 C.F.R. § 1.312 is proper (M.P.E.P. § 714.16). This Amendment is provided in the following format:

(A) A clean version of each replacement paragraph/section/claim along with clear instructions for entry;

(B) Starting on a separate page, appropriate remarks and arguments. 37 C.F.R. § 1.111 and MPEP 714; and

(C) Starting on a separate page, a marked-up version entitled: "Version with markings to show changes made."

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees

for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendment

In the Application:

Please insert the attached sheet of FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D at the end of the application.

In the Specification:

Please insert the following heading after paragraph [0019] and above the heading "DETAILED DESCRIPTION OF THE INVENTION":

BRIEF DESCRIPTION OF THE DRAWINGS

Please insert under the heading "BRIEF DESCRIPTION OF THE DRAWINGS" the following new paragraph:

FIGS. 1A, 1B, 1C, and 1C are voltage pulse protocols used to assess the potency and kinetics of inhibition of the Na^+ channels by the compounds as follows: FIG. 1A: IV-curves, FIG. 1C: steady-state inactivation, FIG. 1B: repriming kinetics, and FIG. 1D: time course of binding.

Please substitute paragraph [0104] at page 20 with the following paragraph:

The following voltage pulse protocols **A**, **B**, **C**, and **D** are used to assess the potency and kinetics of inhibition of the Na^+ channels by the compounds (FIGS. 1A-1D). Current-voltage relationship (IV-curve), protocol **A**, is used to report the voltage at which the maximal inward Na^+ current is achieved. This voltage is used throughout the experiment as testing voltage, V_t. The steady-state inactivation (or, availability) curve, protocol **C**, is used to get the voltage at which almost complete

($\geq$95%) inactivation of Na^+ channels occurs; it serves as voltage for conditioning prepulse, V_c, throughout the experiment. Protocol **B** reports how fast the channels recover from inactivation at hyperpolarized voltages. This permits us to set up the duration of the hyperpolarization gap which is used in measurement of the kinetics of binding of compounds to inactivated Na^+ channels (protocol **D**). Channel repriming under control conditions is fast ($\geq$90% recovery during first 5-10 ms). If a drug substantially retards the repriming process, then it becomes possible (protocol **D**) to accurately measure the kinetics of binding of the inhibitor to inactivated channels as well as the steady-state affinity (k_+ and K_i). To estimate k_+ values, the reduction in peak currents in successive trials with varying pre-pulse duration is plotted as a function of pre-pulse duration and the time constant (τ) measured by mono-exponential fit. A plot of $1/\tau$ as a function of antagonist concentration then allows calculating of the macroscopic binding rates of the antagonists. To determine K_i values the partial inhibition curves measured by fractional responses in steady-state are fitted with the logistic equation:

$$I/I_{control} = 1/(1 + ([antagonist]/K_i)^p), \qquad \text{Eq. 2}$$

where $I_{control}$ is the maximal Na^+ current in the absence of antagonist, [antagonist] is the drug concentration, K_i is the concentration of antagonist that produces half maximal inhibition, and p is the slope factor.

Remarks

None of the amendments add new matter. The amendments merely correct a formal matter without changing the scope of the claims.

The Examiner requested on May 22, 2003, that Fig. 1 on page 20 be deleted and, *in lieu* thereof, inserted at the end of the application. Further, the Examiner requested a new paragraph be added, entitled "Brief Description of the Drawings".

Accordingly, the application has been amended by inserting a sheet of FIGS. 1A-1D at the end of the application that correspond to the original Fig. 1. The symbols A, B, D, and D in the drawing have been amended to read FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D, respectively. No new matter has been added by this amendment.

The specification has been amended by inserting a new paragraph entitled "BRIEF DESCRIPTION OF THE DRAWINGS" after paragraph [0019]. This new paragraph includes the first sentence of paragraph [0104] and the figure text below the Fig. 1. The symbols A, B, D, and D of the figure text have been amended to read FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D, respectively. No new matter has been added by this amendment.

The specification has been also amended by deleting Fig. 1 and the figure text from paragraph [0104] at page 20. Further, paragraph [0104] has been amended by adding --**A**, **B**, **C**, and **D**-- after "protocols" at line 1 of the paragraph and replacing "(Fig. 1)" with --(FIGS. 1A-1D)--. No new matter has been added by these amendments.

Support for the amendments can be found in the original specification as filed. Accordingly, Applicants request that these amendments be entered.

Reconsideration of this application and entry of the above Amendment is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

John M. Covert
Attorney for Applicants
Registration No. 38,759

Date: May 27, 2003

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137,025v1<SKGF_DC1>

Version with markings to show changes made

In the Application:

The attached sheet of FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D has been inserted at the end of the application.

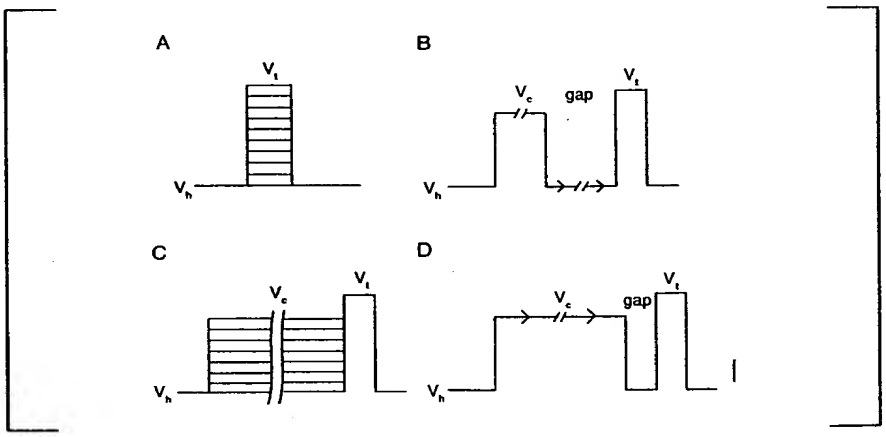
In the Specification:

A heading has been inserted after paragraph [0019] and above the heading "DETAILED DESCRIPTION OF THE INVENTION".

A new paragraph has been inserted under the heading "BRIEF DESCRIPTION OF THE DRAWINGS".

Paragraph [0104] at page 20 has been amended as follows:

The following voltage pulse protocols **A, B, C, and D** are used to assess the potency and kinetics of inhibition of the Na^+ channels by the compounds ([Fig. 1] FIGS. 1A-1D).



[**Figure 1.** Voltage pulse protocols. **A.** IV-curves. **C.** Steady-state inactivation. **B.** Repriming kinetics. **D.** Time course of binding.]

Current-voltage relationship (IV-curve), protocol **A**, is used to report the voltage at which the maximal inward Na^+ current is achieved. This voltage is used throughout the experiment as testing voltage, V_t. The steady-state inactivation (or, availability) curve, protocol **C**, is used to get the voltage at which almost complete ($\geq$95%) inactivation of Na^+ channels occurs; it serves as voltage for conditioning prepulse, V_c, throughout the experiment. Protocol **B** reports how fast the channels recover from inactivation at hyperpolarized voltages. This permits us to set up the duration of the hyperpolarization gap which is used in measurement of the kinetics of binding of compounds to inactivated Na^+ channels (protocol **D**). Channel repriming under control conditions is fast ($\geq$90% recovery during first 5-10 ms). If a drug substantially retards the repriming process, then it becomes possible (protocol **D**) to accurately measure the kinetics of binding of the inhibitor to inactivated channels as well as the steady-state affinity (k_+ and K_i). To estimate k_+ values, the reduction in peak currents in successive trials with varying pre-pulse duration is plotted as a function of pre-pulse duration and the time constant (τ) measured by mono-exponential fit. A plot of $1/\tau$ as a function of antagonist concentration then allows calculating of the macroscopic binding rates of the antagonists. To determine K_i values the partial inhibition curves measured by fractional responses in steady-state are fitted with the logistic equation:

$$I/I_{control} = 1/(1 + ([antagonist]/K_i)^p), \qquad \text{Eq. 2}$$

where $I_{control}$ is the maximal Na^+ current in the absence of antagonist, [antagonist] is the drug concentration, K_i is the concentration of antagonist that produces half maximal inhibition, and p is the slope factor.

FIG. 1A

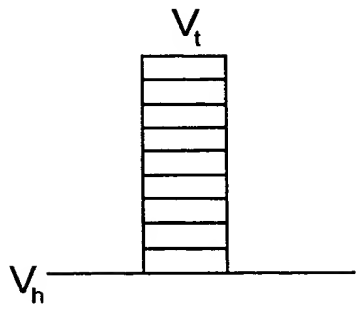


FIG. 1B

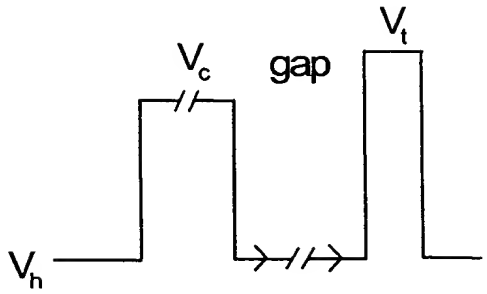


FIG. 1C

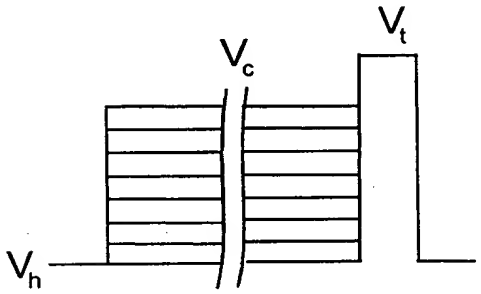
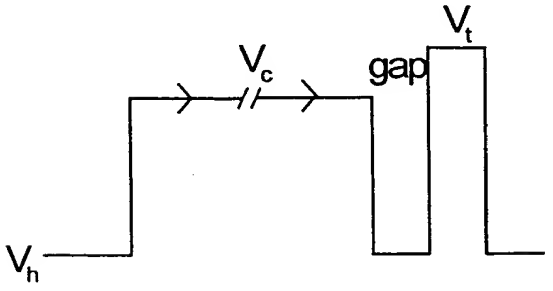


FIG. 1D



		Due Date:	**June 13, 2003**
Applicants:	Hogenkamp *et al.*	**Art Unit:**	1626
		Examiner:	Shameem, G.
Application No.:	09/814,123	**Docket:**	1861.1270001
Filed:	March 22, 2001	**Atty:**	JMC/THN

For: Aryl Substituted Pyrazoles, Triazoles and Tetrazoles, and the Use Thereof

When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following documents:

1. SKGF Cover Letter;
2. Amendment Under 37 C.F.R. § 1.312;
3. One sheet of drawings (Figs. 1A-1D); and
4. One (1) return postcard.

May 27, 2003

Via Hand Carry
Group Art Unit 1626
Examiner G. Shameem

Please Date Stamp And Return To Our Courier

SKGF_DC1:137223.1

		Due Date:	**June 13, 2003**
Applicants:	Hogenkamp *et al.*	**Art Unit:**	1626
		Examiner:	Shameem, G.
Application No.:	09/814,123	**Docket:**	1861.1270001
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Group Art Unit 1626
Examiner G. Shameem

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